ACTA ABP BIOCHIMICA POLONICA

THE 44th FEBS CONGRESS 6-11 JULY 2019 Kraków, Poland

Vol. 66, No 4/2019
483–489
https://doi.org/10.18388/abp.2019_2890

Review

Mesenchymal stem cells' homing and cardiac tissue repair*

Renata Szydlak✉

Chair of Medical Biochemistry, Faculty of Medicine, Jagiellonian University Medical College, Kraków, Poland

Nowadays, mesenchymal stem cells (MSCs) are essential players in cellular therapy and regenerative medicine. MSCs are used to treat cardiac disorders by intramyocardial injection or injection into the bloodstream. Therefore, a premise of successful MSC-based therapy is that the cells reach the site of injury and home the damaged tissue. In response to inflammatory conditions, MSCs can potentially move into the place of injury and colonize damaged tissues, where they participate in their regeneration. This review presents the current knowledge of the mechanisms of MSCs migration and target tissue homing in the field of cardiovascular therapies.

Key words: mesenchymal stem cell, cell migration, tissue repair, cardiovascular diseases, MSC-based therapy

Received: 19 October, 2019; revised: 10 December, 2019; accepted: 10 December, 2019; available on-line: 13 December, 2019

✉e-mail: renata.szydlak@doctoral.uj.edu.pl

***Acknowledgements of financial support**:
The costs of the article published as a part of the 44th FEBS Congress Kraków 2019 – From molecules to living systems block are financed by the Ministry of Science and Higher Education of the Republic of Poland (Contract 805/P-DUN/2019).
This work was supported by a research grant (STRATEGMED2/265761/10/NCBR/2015) from the National Center for Research and Development in Poland.

Abbreviations: AFM, Atomic Force Microscopy; BM-MSCs, Bone Marrow Mesenchymal Stem Cells; CCR, C-C chemokine receptor; CXCR, CXC chemokine receptor; ECM, extracellular matrix; EGF, epidermal growth factor; ERK, Extracellular Signal Regulated Kinase; FAK, Focal Adhesion Kinase; FGF, fibroblast growth factor; FLT-1, fms-like tyrosine kinase 1; HGF, hepatocyte growth factor; HUC-MSC-EXO, Human Umbilical Cord Mesenchymal stem cells-Derived Exosomes; IGF-1, insulin-like growth factor-1; IL-1β, interleukin 1β; IL-6, interleukin 6; IL-8, interleukin 8; ISCT, International Society for Cellular Therapy; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinases; MCP-1, monocyte chemoattractant protein 1; MHC, major histocompatibility complex; MIP-1α, macrophage inflammatory protein; MMP, matrix metalloproteinase; MSC-EXO, Mesenchymal stem cells-Derived Exosomes; MSCs, Mesenchymal Stem Cells; MT1-MMP, Membrane type 1 metalloproteinase ; PDGF, platelet-derived growth factor; PDGFR, platelet derived growth factor receptor; PI3K, Phosphoinositide 3-kinases; SDF-1, stromal cell-derived factor-1; sFRP2, Secreted Frizzled Related Protein 2; TGF-β, transforming growth factor β; TNF-α, tumor necrosis factor-α; VCAM, vascular cell adhesion molecule; ICAM, intercellular adhesion molecule; VEGF, vascular endothelial growth factor; VLA-4, Very Late Antigen-4; WJ-MSCs, Wharton's Jelly Mesenchymal Stem Cells

INTRODUCTION

Mesenchymal stem cells (MSCs) represent a population of undifferentiated cells, multipotent, with the ability to self-renew and differentiate into many cell types. They carry markers similar to those of tissue fibroblasts and are difficult to distinguish from them. For the first time, Friedenstein and others (Friedenstein *et al.*, 1970) described bone marrow-derived fibroblast-like cells which later became the most extensively studied MSCs. Subsequently these cells were also found in the adipose tissue, muscle, dental pulp, periosteum, synovium, and synovial fluid, tendons, endometrium, skin, lungs, chorionic villi, peripheral blood, menstrual blood, breast milk, as well as in umbilical cord, Wharton's jelly, placenta, and umbilical cord blood (Eleuteri & Fierabracci, 2019; Berebichez-Fridman & Montero-Olvera, 2018; Kong *et al.*, 2019).

The minimum criteria to be fulfilled by a cell to be classified as a mesenchymal stem cell were stated in a paper published by the International Society for Cellular Therapy (ISCT) in 2006 (Dominici *et al.*, 2006). As per this statement, cells need to satisfy three conditions to be recognized as MSC (Table 1). Even though a wide range of selection markers defining MSCs were identified, no single marker specific only to them has been indicated.

In response to inflammatory conditions, MSCs can potentially move into the site of injury and colonize the damaged tissues, where they participate in their regeneration (Murphy *et al.*, 2013; Rosenthal, 2003). The efficacy of MSC-based therapy depends on their homing ability and engraftment into the target tissue. The possibility of using MSCs in the therapy of many diseases needs to be preceded, though, by an in-depth analysis of their properties, especially by determining the mechanism of tissue homing, as well as the mechanism due to which the cells contribute to tissue regeneration.

This review presents the current knowledge of the mechanisms of MSCs migration, homing, and cardiac tissue regeneration, hoping to develop an effective treatment for cardiovascular diseases and many other clinical applications.

Table 1. General characteristics of mesenchymal stem cells.

Morphology	Spindle-shaped, fibroblast-like
Growth properties	adherent
Surface markers	$CD73^+$, $CD90^+$, $CD105^+$, $CD11b^-$, $CD14^-$, $CD19^-$, $CD45^-$, $CD79\alpha^-$, $HLA\text{-}DR^-$, $MHC\text{-}II^-$
In vitro differentiation potential	osteogenic, chondrogenic, adipogenic

WHY MSCs?

MSCs can be of great significance for healing tissue damage owing to their distribution in a wide range of tissues, their differentiation potential, and the reparative effects noticed when MSCs are infused in pre-clinical and clinical models (Wei *et al*., 2013). It is widely accepted that there are roles for MSCs in tissue growth, wound healing, and maintenance of the cell supply to compensate for the cells' lost due to apoptosis and pathology. Due to these roles, researchers and clinicians have used MSCs for treating tissue damage.

Numerous studies were performed, indicating the effectiveness of MSCs' application to decrease the postinfarction myocardial scarring and restore regular systolic function in case of acute myocardial infarction (Afzal *et al*., 2015; Majka *et al*., 2017). MSCs exhibit high chemotaxis into damaged tissues, and areas embodied with inflammatory reaction and oxygen deficiency, thus conditions dominating in ischemic damaged tissue of cardiac muscle (Sohni & Verfaillie, 2013). However, the exact mechanism due to which the cells contribute to regeneration of the cardiac muscle is still unknown. Supposedly, this process depends on many factors and probably does rely on a direct ability of MSCs to diversify towards cardiomyocytes, but on their ability to release cytokines and growth factors with trophic properties (Gnecchi & Cervio, 2013; Yamahara & Nagaya, 2007). Among fundamental mechanisms of mesenchymal stem cells action, the most important is secretion of the paracrine factors and integration at the cellular level (Markel *et al*., 2008; Mirotsou *et al*., 2007; Karantalis & Hare, 2015). MSCs can also contribute to attenuation of inflammatory conditions and stimulation of endogenous repair mechanisms through their immunosuppressive properties (Hamid & Prabhu, 2017; Kocher *et al*., 2001; Ward *et al*., 2018).

MSCs secrete TNF-α, IL-6, and IL-8 cytokines suggested as potential mediators of heart preservation (Hatzistergos *et al*., 2010; Molina *et al*., 2009). It was demonstrated that proinflammatory cytokines increase immunity of cardiomyocytes to ischemia (Molina *et al*., 2009). Additionally, IL-8 is known to influence cell proliferation and angiogenesis. MSCs also secrete growth factors, including granulocyte and macrophage colony-stimulating factors, as well as the FMS-like tyrosine kinase 3 (Hodgkinson *et al*., 2016). Growth factors are capable of inducing myocardium by restraining apoptosis of cardiomyocytes in the implantation area, and further secreting antiapoptotic and angiogenic factors, such as the vascular endothelial growth factor (VEGF) that stimulates angiogenesis (Markel *et al*., 2008) and sFRP2 protein that modulates the Wnt signaling pathway (Mirotsou *et al*., 2007). Secretion of angiogenic factors is crucial for neovascularization of the cardiac muscle after heart attack, as mesenchymal stem cells lacking VEGF are less efficient at myocardial regeneration after injury (Markel *et al*., 2008).

In addition to cytokines, mesenchymal stem cells also secrete metalloproteinases which reorganize the extracellular matrix (ECM) in the scar tissue (Molina *et al*., 2009). Reversed remodeling of the scar tissue and antifibrotic effects in the necrotic tissue of the heart muscle are essential for regeneration and functional restoration of the heart after myocardial infarction. Further, mesenchymal stem cells stimulate the proliferation and differentiation of endogenous cardiac stem cells, simultaneously contributing to the cardiac muscle regeneration (Hatzistergos *et al*., 2010).

Moreover, MSCs also immediately interact with other cell types through interactions at the cellular level. Owing to direct and intermediate cell communication and signaling with cells in the damaged areas, MSCs recruit other stem cells to facilitate regeneration of the damaged tissue. An excellent example of the mentioned type of interactions is the signaling pathway SDF-1α/CXCR4 that regulates cell migration of hematopoietic stem cells to the damaged myocardium (Elmadbouh *et al*., 2007; Zhang *et al*., 2007).

MSCs can also serve as an exosome provider (Lai *et al*., 2015). Exosomes play an essential role in cellular communication and change biochemical characteristics of the recipient cells by providing biomolecules (Wang *et al*., 2018). These bubbles are produced from body fluids and various cell types, such as MSCs (Zeringer *et al*., 2015). Evidence suggests that the mesenchymal stem cells-derived exosome (MSC-EXO) has MSC-like functions with low immunogenicity and no carcinogenic potential. Studies performed by Zhao *et al*. in a rat model of acute myocardial infarction have shown that the use of HUC-MSC-EXO and micro-vesicles can improve cardiac function after four weeks of HUC-MSC-EXO injection (Zhao *et al*., 2015). Also, reduced cardiac fibrosis was observed after Masson's trichrome staining.

RECRUITMENT AND HOMING OF MSCs

Molecular factors involved in MSCs migration

A premise of successful MSC-based therapy is that the cells reach the site of injury and home the damaged tissue, which is possible due to their ability to reach the damaged places thanks to their ability to migrate, adhere, and get implanted into the target tissue. Therapeutic efficacy and target tissue homing by MSCs are influenced by several factors, such as the source of the cells, the age of the donor, breeding conditions, the number of passages, method of supplying cells, the number of cells implanted, general condition and susceptibility of the host (Beane *et al*., 2014; Siegel *et al*., 2013; Izadpanah *et al*., 2008; Zhuang *et al*., 2015). It has been proven that freshly isolated cells have higher engraftment in tissue and more efficient target tissue homing when compared to cells from long-term *in vitro* expansion (Rombouts & Ploemacher, 2003; Hong *et al*., 2019). This probably results from aging and differentiation of MSCs during *in vitro* cultivation (Trounson & McDonald, 2015). Culture conditions also have a significant impact on the MSCs homing, as they can modify expression of the surface markers involved in this process (Yang *et al*., 2018).

The site and method used for administration of MSCs for therapeutic purposes can influence the way taken by cells to reach the desired destination (Boltze *et al*., 2015). Usually, MSCs are administrated systemically by injection into the bloodstream. Therefore, the necessary condition for an effective therapy based on MSCs is the capacity of the used cells to get to the site of injury and to occupy tissue affected by the disease. The remedial effect is most likely a result of increased migration of cells towards the damaged tissue, preceded by MSCs adhesion to vascular endothelial cells.

Many studies have shown that MSCs are capable of directional migration in response to inflammatory conditions (Nakajima *et al*., 2012; Zachar *et al*., 2016; Yagi *et al*., 2010). MSCs are thought to use the same mechanism of migration into a tissue as leukocytes (Nitzsche *et al*., 2017). However, in contrast to the well-described

mechanisms of leukocyte adhesion and movement, the mechanism of tissue homing by MSCs is not yet fully understood, despite the fact that there are numerous studies assessing MSCs adhesive molecules and possible mechanisms of vascular wall adhesion and migration, as well as evaluating the role of chemokines in guiding MSCs to the target tissues (Kia *et al.*, 2011; Ghaffari-Nazari, 2018).

Before MSCs migrate through the wall of a vessel, they are rolling on its surface, finding the best place for adhesion and then transmigrating through the endothelium (Fig. 1) (Nitzsche *et al.*, 2017). The interaction of integrins that are expressed in the MSCs' cell membrane with adhesion molecules at the endothelial surface (VCAM and ICAM) can lead to formation of docking structures and transmigration wells that are rich in ICAM-1, VCAM-1, proteins, and cytoskeleton components (Nitzsche *et al.*, 2017; De Becker & Van Riet, 2016).

To date, several molecules involved in interactions between MSCs and endothelial cells were indicated, including VLA-4, VCAM-1, ICAM-1, and P-selectin. Adhesion molecules, such as selectins, integrins, and chemokine receptors, are committed to rolling, adhesion, and transmigration of MSCs. Mesenchymal stem cells have been shown to express various receptors associated with intercellular contacts and adherence to extracellular matrix proteins, such as α1, α2, α3, α4, α5, αv, β1, β3 and β4 integrins, and other adhesion molecules, i.e. VCAM-1, ICAM-1, ICAM-3, CD166 (ALCAM) (Rüster *et al.*, 2006; Ip *et al.*, 2007). Some studies have shown that MSCs adhesion to the endothelium occurs with participation of P-selectin. It has been observed that MSCs may use new carbohydrate ligands to interact with P-selectin on the endothelial surface (Rüster *et al.*, 2006). Steingen *et al.* reported that MSCs could migrate through endothelium using the VLA-4/VCAM-1 complex, and that MSCs tend to integrate with the endothelial layer instead of passing full diapedesis (Steingen *et al.*, 2008). Among the integrin family, a key role in adhesion, migration, and chemotaxis is played by integrin α4β1, which is a mediator in the cell-cell contact and cell-environment interactions. However, because the MSCs' transendothelial migration has not been entirely blocked by the anti-VLA4 antibody and the anti-VCAM-1 antibody, it can be assumed that other integrins are also involved in this process (Steingen *et al.*, 2008).

Although integrins and selectins play an essential role in transmigration of MSCs, chemokines released from the tissues and endothelial cells can promote activation of ligands involved in adhesion, migration, chemotaxis and homing of MSCs in the target tissues. Many reports suggest that the damaged tissue releases specific factors that act as chemoattractants to facilitate adhesion, movement, and homing of MSCs in the affected areas (Nakajima *et al.*, 2012; Zachar *et al.*, 2016; Yagi *et al.*, 2010). Studies have shown that MSCs are capable of migrating to the inflamed tissues in response to factors that are regulated under inflammatory conditions. So far, many chemokines and growth factors have been identified that are involved in the migration process. These are proinflammatory cytokines, such as TNF-α, IL-1β, IL-6, IL-8, and many growth factors, e.g., EGF, FGF, HGF, IGF-1, PDGF-AB, SDF-1α, TGF-B1, VEGF-A (Fox *et al.*, 2007; Honczarenko *et al.*, 2005; Kortesidis *et al.*, 2005; Leibacher & Henschler, 2016; Guo *et al.*, 2018). Some studies have shown expression of chemokine receptors by MSCs, including CXCR1–CXCR6, CCR1–CCR10, and have pointed to functional roles of some of them in the MSCs migration process (Honczarenko *et al.*, 2005; Ringe *et al.*, 2007; Lüttichau *et al.*, 2005; Sordi *et al.*, 2005). It has been proven that CXCR1, CXCR2, CXCR4, CCR1, CCR2, IL-8, MIP-1α, and MCP-1 are involved in migration of MSCs into the damaged tissue (Eseonu & De Bari, 2015). Other studies have shown that the SDF-1/CXCR4 axis plays a vital role in the movement of MSCs isolated from the bone marrow (Su *et al.*, 2017; Kitaori *et al.*, 2009). Therefore, it is likely that chemokines released from tissues cause expression of the CXCR4 receptor, which contributes to migration of MSCs to their final destination. It has been also shown that an increase in IL-8 concentration in the damaged tissues can activate the MSCs migration (Ringe *et al.*, 2007). An active role of IL-6, PDGF, PDGFR-α PDGFR-β, vascular endothelial growth factor receptor 1 (FLT-1), and IGF-1 was indicated in the BM-MSCs migration studies (Eseonu & De Bari, 2015). PDGFR has been highly expressed in the BM-MSCs, and PDGF induces BM-MSCs migration. A migration test through a porous filter also showed that PDGF has a stronger effect on MSCs chemotaxis than SDF-1 and MCP-1 (Lee *et al.*, 2012). According to those studies, numerous chemokines play a role in induction of MSCs migration, but details, including mechanisms of colonization by MSCs, require further *in vitro* and *in vivo* studies.

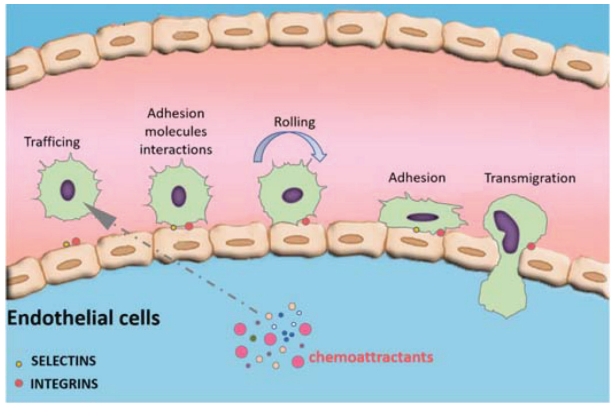

Figure 1. A potential mechanism of MCSs migration across the endothelium [source: https://periobasics.com/mechanisms-of-transendothelial-migration-of-leukocytes.html; modified; access on 19.09.2019].

An important role played by proteolytic enzymes – metalloproteinases which regulate the extracellular matrix degradation, has been also confirmed (Steingen *et al.*, 2008; De Becker *et al.*, 2007; Ries *et al.*, 2007). Different MMPs and their signaling pathways have been shown to affect MSCs differentiation, migration, angiogenesis, and proliferation. Migration and invasion of MSCs into damaged tissues are facilitated by expression of CXCR4, MMP-2, and MT1-MMP (Almalki & Agrawal, 2016). Inflammatory cytokines, such as IL-1β and TNF-α, stimulate production of MMPs by MSCs and activate chemotactic migration through the extracellular matrix (Sohni & Verfaillie, 2013).

Mechanical cues regulating MSCs movement

During migration through peripheral blood circulation towards the damaged tissue, exogenous MSCs injected into the body are exposed to various hemodynamic forces applied to the vessel walls, including shear stress and cyclic mechanical load. It has been observed that mechanical loads affect migration of MSCs. Studies by Zhang and others (Zhang *et al.*, 2015) have shown that

cyclic mechanical stretching (10%, 8 hours) promotes MSCs migration through the FAK-ERK1/2 pathway, but leads to a decrease in the invasive potential of MSCs by downregulating MT1 – MMP *via* the PI3K/Act signaling pathway (Zhang *et al*., 2015; Fu *et al*., 2019).

Shear stress is another type of force inside the blood vessels. However, so far only a few studies have focused on the effects of shear stress on MSCs movement. It was observed that shear stress (~0.2 Pa) promoted MSCs migration in the wound healing test, while a higher shear stress (> 2 Pa) had significantly inhibited MSCs migration by regulating the JNK and p38 MAPK pathways (Yuan *et al*., 2012).

The ability of the cell to dynamically reshape is essential for migratory behavior due to physical limitations in the tissue (Rudzka *et al*., 2019; Xu *et al*., 2012). How a given cell remodels its shape is related to the cell deformability, and cell elasticity depends on the structure of the cytoskeleton (Olson & Sahai, 2009). Our recent studies have proven that the elasticity of MSCs observed by atomic force microscopy (AFM) is an important factor that determines the ability of MSCs to migrate across a porous filter (Szydlak *et al*., 2019). The results have shown that MSCs with the potential of transendothelial migration and invasion were characterized by higher deformability (Szydlak *et al*., 2019). Previous studies performed by McGrail *et al*. have demonstrated that loss of MSCs elasticity leads to a decrease in MSCs motility in the wound healing assay and transmigration tests (McGrail *et al*., 2013).

Furthermore, mechanical properties of the microenvironment, such as the extracellular matrix elasticity, and mechanical and shear stresses occurring in the blood vessels, are crucial in MSCs migration. Biophysical signals that reach MSCs play an essential role in regulating their behavior.

Previous studies focused on the effect of extracellular matrix rigidity on MSCs migration. The research conducted by Raab *et al*. showed that MSCs migrated from a soft substrate (1 kPa) towards the rigid surface (34 kPa) by cytoskeleton polarization and myosin-IIB heavy chain phosphorylation (myosin-IIB) (Raab *et al*., 2012), which suggests that mechanical properties of the substrate are regulating the MSCs polarization and migration. Other studies, conducted by Vincent *et al*., constructed substrates with a stiffness gradient that was intended to simulate natural changes in the tissue stiffness, pathological changes, and tissues showing abrupt changes in stiffness. The results of this experiment showed that MSCs migrated towards stiffer fragments, using the actin cytoskeleton for this purpose, and directional migration was carried out using microtubules (Vincent *et al*., 2013).

The studies of the mechanism of MSCs' migration are crucial for the development of MSC-based therapies because their ability to reach target tissue is a key factor in achieving therapeutic effectiveness. After recruitment and migration into the damaged tissues, MSCs will play their role and promote damaged tissue repair and organ regeneration, as well as reverse progression of the disease.

FUTURE DIRECTIONS

Despite promising results of clinical trials involving MSCs, there are ongoing efforts to increase the effectiveness of MSCs, primarily because effects observed in the preclinical studies are stronger than in the clinical ones. Standardization of stem cell acquisition and culture methods is one of the fundamental challenges of modern cell therapy, and MSCs cell isolation and culture protocols to enhance safety of their *in vivo* use still require refinement. In addition, various methods are tested to increase the effectiveness of MSCs *in vivo*. They include a combination of MSCs therapy with standard pharmacotherapy (Ascheim *et al*., 2014), genetic engineering techniques (Bobis-Wozowicz *et al*., 2011), biomaterials engineering (Sekula *et al*., 2017), MSCs pre-conditioning, e.g. by reducing oxygen availability (Ejtehadifar *et al*., 2015) or using an inflammatory factor (Hahn *et al*., 2008).

Although many studies (both preclinical and clinical) show more and more evidence of the therapeutic effectiveness of MSCs, the main problem that remains is the low degree of retention of MSCs in the tissues due to their short-lived viability after implantation into the recipient's body (Von Bahr *et al*., 2012). The immune status of the patient before and after injection determines survival of the implanted allogeneic MSCs. *In vivo* experiments have shown that the time of MSCs transplantation decides on their therapeutic effect in a model of myocardial infarction (Hu *et al*., 2007). Rigol *et al*. observed that MSCs induce better neovascularization and better long-term prognosis when injected 15 minutes after reperfusion than those injected a week later (Rigol *et al*., 2014). It has been detected that less than 10% of MSCs are retained in the damaged tissue 24 hours after injection into the body, and only about 1% is still at the site of injury after four weeks (Lee *et al*., 2011). In addition, it has been shown that after MSCs transplantation, many of them become trapped in the capillaries of the lungs, which reduces the population of cells occupying the target tissue (Rigol *et al*., 2014), and only a part of MSCs population responds to inflammatory factors and reaches the damaged tissue, e.g., in the case of infarcted myocardium or ischemic damaged brain (Von Bahr *et al*., 2012; Barzegar *et al*., 2019). This problem was attempted to be solved by repeated MSCs injections. However, it was observed that such a repeated administration might cause production of immune alloantibodies (Cho *et al*., 2008). Therefore, one of the biggest challenges faced by MSC-based therapies is to improve engraftment efficiency.

An important factor is also the change in the expression of some adhesive molecules that occurs during long-term *in vitro* culture (Phinney & Prockop, 2007; De Becker *et al*., 2007). It has been observed that the *in vitro* expansion of MSCs gradually leads to a loss of expression of homing molecules and, in consequence, to a loss of tissue homing capacity by MSCs (Honczarenko *et al*., 2005; Rombouts & Ploemacher, 2003).

The method of administration of MSCs can be an essential factor in achieving the intended destination. Researchers have tested many ways of providing MSCs that aim to ensure that these cells are successfully homed in the areas of ischemia, to prolong survival in the body in an inflammatory environment that will eventually lead to successful neovascularization. Also, non-invasive methods are considered due to the risks associated with operational procedures. For example, in the treatment of brain damage, injecting MSCs directly into a damaged brain can bring high efficacy in therapy, but involves the risk of surgical complications that can be minimized by using less invasive or non-invasive techniques, or by systemic administration. New methods of stem cell delivery are currently being tested. These include such techniques as genetic modification of MSCs and cell surface engineering, *in vitro* pre-conditioning, and target tissue modification, as well as biomaterial engineering and cell scaffolding construction (Chen *et al*., 2018). In addition,

methods such as targeted administration, magnetic and ultrasound guidance, and radiotherapy techniques are being tested (Fakoya, 2017). The advantage of selective injection of these cells is reduced cell loss during cell delivery and migration, when compared to systemic administration (Kim *et al.*, 2014).

On the other hand, the methods for labeling and detection of MSCs *in vivo* after transplantation still need improvement. Despite promising results of *in vitro* studies, there is lack of data about the behavior of MSCs after transplantation. That is why it is so important to be able to monitor the distribution, survival, and function of MSCs after *in vivo* transplantation, especially in patients. These needs have led to remarkable advances in molecular imaging, including magnetic resonance imaging, scintigraphy, PET, optical imaging, and ultrasound, as well as multimodal imaging (Bose & Mattrey, 2019). Stem cell labeling with reporter genes or reporters to enable their detection and evaluation of their *in vivo* function was achieved using all current imaging methods with promising results in preclinical results and with some success in clinical trials as well (Wang & Jokerst, 2016). However, currently there is no ideal approach to MSC imaging, each having advantages and limitations.

CONCLUDING REMARKS

The magical ability to regenerate damaged parts of the body to regain a lost function has been a dream of humanity for a long time. MSC-based therapy is still an innovative and clinically needed therapeutic concept. The three properties of MSC make them optimal for tissue regeneration: (1) immunoregulatory ability is beneficial in alleviating abnormal immune responses, (2) paracrine or autocrine functions that generate growth factors, and (3) the ability to differentiate into target cells. Despite promising results of many studies, the biggest challenge of MSC-based therapies is to increase the target tissue retention. There is still need for basic research that will allow us to fully understand the *in vivo* mechanisms of MSCs in the future. The proposed scheme of the relationship between MSC migration and tissue repair is based on a chemotactic hypothesis. In response to inflammatory conditions, MSCs can potentially move into the site of injury and colonize the damaged tissues, where they participate in their regeneration. To date, many various factors have been recognized that affect MSCs migration, but the detailed mechanism involved in this proses is not yet fully understood. Answers to these questions would provide valuable information for further research and effective cellular therapy.

Acknowledgments

The author is grateful to Prof. Piotr Laidler who moderated this paper and in that line significantly improved this manuscript. This paper would not have been possible without the substantive support of Prof. Marcin Majka.

Conflicts of Interest

The author declares no conflict of interest.

REFERENCES

Afzal MR, Samanta A, Shah ZI, Jeevanantham V, Abdel-Latif A, Zuba-Surma EK, Dawn B (2015) Adult bone marrow cell therapy for ischemic heart disease: Evidence and insights from randomized controlled trials. *Circ. Res.* **117**: 558–575. https://doi.org/10.1161/CIRCRESAHA.114.304792

Almalki SG, Agrawal DK (2016) Effects of matrix metalloproteinases on the fate of mesenchymal stem cells. *Stem Cell Res. Ther.* **7**: 129. https://doi.org/10.1186/s13287-016-0393-1

Ascheim DD, Gelijns AC, Goldstein D, Moye LA, Smedira N, Lee S, Klodell CT, Szady A, Parides MK, Jeffries NO, Skerrett D, Taylor DA, Rame JE, Milano C, Rogers JG, Lynch J, Dewey T, Eichhorn E, Sun B, Feldman D, Simari R, O'Gara PT, Taddei-Peters WC, Miller MA, Naka Y, Bagiella E, Rose EA, Woo YJ (2014) Mesenchymal precursor cells as adjunctive therapy in recipients of contemporary left ventricular assist devices. *Circulation* **129**: 2287–2296 https://doi.org/10.1161/CIRCULATIONAHA.113.007412

Von Bahr L, Batsis I, Moll G, Hägg M, Szakos A, Sundberg B, Uzunel M, Ringden O, Le Blanc K (2012) Analysis of tissues following mesenchymal stromal cell therapy in humans indicates limited long-term engraftment and no ectopic tissue formation. *Stem Cells* **30**: 1575–1578. https://doi.org/10.1002/stem.1118

Barzegar M, Kaur G, Gavins FNE, Wang Y, Boyer CJ, Alexander JS (2019) Potential therapeutic roles of stem cells in ischemia-reperfusion injury. *Stem Cell Res.* **37**: 101421 https://doi.org/10.1016/j.scr.2019.101421

Beane OS, Fonseca VC, Cooper LL, Koren G, Darling EM (2014) Impact of aging on the regenerative properties of bone marrow-, muscle-, and adipose-derived mesenchymal stem/stromal cells. *PLoS One* **9**: e115963. https://doi.org/10.1371/journal.pone.0115963

De Becker A, Van Hummelen P, Bakkus M, Broek I Vande, De Wever J, De Waele M, Van Riet I (2007) Migration of culture-expanded human mesenchymal stem cells through bone marrow endothelium is regulated by matrix metalloproteinase-2 and tissue inhibitor of metalloproteinase-3. *Haematologica* **92**: 440–449. https://doi.org/10.3324/haematol.10475

De Becker A, Van Riet I (2016) Homing and migration of mesenchymal stromal cells: How to improve the efficacy of cell therapy? *World J. Stem Cells* **8**: 73–87. https://doi.org/10.4252/wjsc.v8.i3.73

Berebichez-Fridman R, Montero-Olvera PR (2018) Sources and clinical applications of mesenchymal stem cells state-of-the-art review. *Sultan Qaboos Univ. Med. J.* **18**: e264–e227. https://doi.org/10.18295/squmj.2018.18.03.002

Bobis-Wozowicz S, Miekus K, Wybieralska E, Jarocha D, Zawisz A, Madeja Z, Majka M (2011) Genetically modified adipose tissue-derived mesenchymal stem cells overexpressing CXCR4 display increased motility, invasiveness, and homing to bone marrow of NOD/SCID mice. *Exp. Hematol.* **39**: 686–696. https://doi.org/10.1016/j.exphem.2011.03.004

Boltze J, Arnold A, Walczak P, Jolkkonen J, Cui L, Wagner DC (2015) The dark side of the force – constraints and complications of cell therapies for stroke. *Front. Neurol.* **6**: 155. https://doi.org/10.3389/fneur.2015.00155

Bose RJC, Mattrey RF (2019) Accomplishments and challenges in stem cell imaging *in vivo*. *Drug Discov. Today* **24**: 492–504. https://doi.org/10.1016/j.drudis.2018.10.007

Chen Z, Chen L, Zeng C, Wang WE (2018) Functionally improved mesenchymal stem cells to better treat myocardial infarction. *Stem Cells Int.* **2018**:7045245. https://doi.org/10.1155/2018/7045245

Cho PS, Messina DJ, Hirsh EL, Chi N, Goldman SN, Lo DP, Harris IR, Popma SH, Sachs DH, Huang CA (2008) Immunogenicity of umbilical cord tissue-derived cells. *Blood* **111**: 430–438. https://doi.org/10.1182/blood-2007-03-078774

Dominici M, Le Blanc K, Mueller I, Slaper-Cortenbach I, Marini F, Krause D, Deans R, Keating A, Prockop D, Horwitz E (2006) Minimal criteria for defining multipotent mesenchymal stromal cells. The International Society for Cellular Therapy position statement. *Cytotherapy* **8**: 315–317. https://doi.org/10.1080/14653240600855905

Ejtehadifar M, Shamsasenjan K, Movassaghpour A, Akbarzadehlaleh P, Dehdilani N, Abbasi P, Molaeipour Z, Saleh M (2015) The effect of hypoxia on mesenchymal stem cell biology. *Adv. Pharm. Bull.* **5**: 141–149. https://doi.org/10.15171/apb.2015.021

Eleuteri S, Fierabracci A (2019) Insights into the secretome of mesenchymal stem cells and its potential applications. *Int. J. Mol. Sci.* **20** 18. https://doi.org/10.3390/ijms20184597

Elmadbouh I, Haider HK, Jiang S, Idris NM, Lu G, Ashraf M (2007) *Ex vivo* delivered stromal cell-derived factor-1α promotes stem cell homing and induces angiomyogenesis in the infarcted myocardium. *J. Mol. Cell. Cardiol.* **42**: 792–803. https://doi.org/10.1016/j.yjmcc.2007.02.001

Eseonu OI, De Bari C (2015) Homing of mesenchymal stem cells: mechanistic or stochastic? Implications for targeted delivery in arthritis. *Rheumatol. (United Kingdom)* **54**: 210–218. https://doi.org/10.1093/rheumatology/keu377

Fakoya AOJ (2017) New delivery systems of stem cells for vascular regeneration in ischemia. *Front. Cardiovasc. Med.* **4**: 7. https://doi.org/10.3389/fcvm.2017.00007

Fox JM, Chamberlain G, Ashton BA, Middleton J (2007) Recent advances into the understanding of mesenchymal stem cell traffick-

ing. *Br. J. Haematol.* **137**: 491–502. https://doi.org/10.1111/j.1365-2141.2007.06610.x
Friedenstein AJ, Chailakhjan RK, Lalykina KS (1970) The development of fibroblast colonies in monolayer cultures of guinea-pig bone marrow and spleen cells. *Cell Prolif.* **3**: 393–340. https://doi.org/10.1111/j.1365-2184.1970.tb00347.x
Fu X, Halim A, Tian B, Luo Q, Song G (2019) MT1-MMP down-regulation via the PI3K/Akt signaling pathway is required for the mechanical stretching-inhibited invasion of bone-marrow-derived mesenchymal stem cells. *J. Cell. Physiol.* **234**: 14133–14144. https://doi.org/10.1002/jcp.28105
Ghaffari-Nazari H (2018) The known molecules involved in MSC homing and migration. *J. Stem Cell Res. Med.* **3**: 1–4. https://doi.org/10.15761/jscrm.1000127
Gnecchi M, Cervio E (2013) Mesenchymal stem cell therapy for heart disease. In: *Mesenchymal Stem Cell Therapy,* pp 241–270. https://doi.org/10.1007/978-1-62703-200-1_13
Guo YC, Chiu YH, Chen CP, Wang HS (2018) Interleukin-1β induces CXCR3-mediated chemotaxis to promote umbilical cord mesenchymal stem cell transendothelial migration. *Stem Cell Res. Ther.* **9**: 281. https://doi.org/10.1186/s13287-018-1032-9
Hahn JY, Cho HJ, Kang HJ, Kim TS, Kim MH, Chung JH, Bae JW, Oh BH, Park YB, Kim HS (2008) Pre-treatment of mesenchymal stem cells with a combination of growth factors enhances gap junction formation, cytoprotective effect on cardiomyocytes, and therapeutic efficacy for myocardial infarction. *J. Am. Coll. Cardiol.* **51**: 933–943. https://doi.org/10.1016/j.jacc.2007.11.040
Hamid T, Prabhu SD (2017) Immunomodulation is the key to cardiac repair. *Circ. Res.* **120**: 1530–1532. https://doi.org/10.1161/circresaha.117.310954
Hatzistergos KE, Quevedo H, Oskouei BN, Hu Q, Feigenbaum GS, Margitich IS, Mazhari R, Boyle AJ, Zambrano JP, Rodriguez JE, Dulce R, Pattany PM, Valdes D, Revilla C, Heldman AW, McNiece I, Hare JM (2010) Bone marrow mesenchymal stem cells stimulate cardiac stem cell proliferation and differentiation. *Circ. Res.* **107**: 913–922. https://doi.org/10.1161/CIRCRESAHA.110.222703
Hodgkinson CP, Bareja A, Gomez JA, Dzau VJ (2016) Emerging concepts in paracrine mechanisms in regenerative cardiovascular medicine and biology. *Circ. Res.* **118**: 95–107. https://doi.org/10.1161/CIRCRESAHA.115.305373
Honczarenko M, Le Y, Swierkowski M, Ghiran I, Glodek AM, Silberstein LE (2005) Human bone marrow stromal cells express a distinct set of biologically functional chemokine receptors. *Stem Cells* **24**: 1030–1041. https://doi.org/10.1634/stemcells.2005-0319
Hong SH, Lee MH, Koo MA, Seon GM, Park YJ, Kim D, Park JC (2019) Stem cell passage affects directional migration of stem cells in electrotaxis. *Stem Cell Res.* **38**: 101475. https://doi.org/10.1016/j.scr.2019.101475
Hu X, Wang J, Chen J, Luo R, He A, Xie X, Li J (2007) Optimal temporal delivery of bone marrow mesenchymal stem cells in rats with myocardial infarction. *Eur. J. Cardio-thoracic Surg.* **31**: 438–443. https://doi.org/10.1016/j.ejcts.2006.11.057
Ip JE, Wu Y, Huang J, Zhang L, Pratt RE, Dzau VJ (2007) Mesenchymal stem cells use integrin β1 not CXC chemokine receptor 4 for myocardial migration and engraftment. *Mol. Biol. Cell* **18**: 2873–2882 .https://doi.org/10.1091/mbc.E07-02-0166
Izadpanah R, Kaushal D, Kriedt C, Tsien F, Patel B, Dufour J, Bunnell BA (2008) Long-term *in vitro* expansion alters the biology of adult mesenchymal stem cells. *Cancer Res.* **68**: 4229–4238. https://doi.org/10.1158/0008-5472.CAN-07-5272
Karantalis V, Hare JM (2015) Use of mesenchymal stem cells for therapy of cardiac disease. *Circ. Res.* **116**: 1413-1430. https://doi.org/10.1161/CIRCRESAHA.116.303614
Kia NA, Bahrami AR, Ebrahimi M, Matin MM, Neshati Z, Almohaddesin MR, Aghdami N, Bidkhori HR (2011) Comparative analysis of chemokine receptor's expression in mesenchymal stem cells derived from human bone marrow and adipose tissue. *J. Mol. Neurosci.* **44**: 178–185. https://doi.org/10.1007/s12031-010-9446-6
Kim I, Bang SI, Lee SK, Park SY, Kim M, Ha H (2014) Clinical implication of allogenic implantation of adipogenic differentiated adipose-derived stem cells. *Stem Cells Transl. Med.* **3**: 1312–1321. https://doi.org/10.5966/sctm.2014-0109
Kitaori T, Ito H, Schwarz EM, Tsutsumi R, Yoshitomi H, Oishi S, Nakano M, Fujii N, Nagasawa T, Nakamura T (2009) Stromal cell-derived factor 1/CXCR4 signaling is critical for the recruitment of mesenchymal stem cells to the fracture site during skeletal repair in a mouse model. *Arthritis Rheum.* **60**: 813–823. https://doi.org/10.1002/art.24330
Kocher AA, Schuster MD, Szabolcs MJ, Takuma S, Burkhoff D, Wang J, Homma S, Edwards NM, Itescu S (2001) Neovascularization of ischemic myocardium by human bone-marrow-derived angioblasts prevents cardiomyocyte apoptosis, reduces remodeling and improves cardiac function. *Nat. Med.* **7**: 430–436. https://doi.org/10.1038/86498
Kong CM, Lin HD, Biswas A, Bongso A, Fong CY (2019) Manufacturing of human Wharton's jelly stem cells for clinical use: selection of serum is important. *Cytotherapy* **21**: 483–495. https://doi.org/10.1016/j.jcyt.2019.02.008
Kortesidis A, Zannettino A, Isenmann S, Shi S, Lapidot T, Gronthos S (2005) Stromal-derived factor-1 promotes the growth, survival, and development of human bone marrow stromal stem cells. *Blood* **105**: 3793–3801. https://doi.org/10.1182/blood-2004-11-4349
Lai RC, Yeo RWY, Lim SK (2015) Mesenchymal stem cell exosomes. *Semin. Cell Dev. Biol.* **40**: 82–88. https://doi.org/10.1016/j.semcdb.2015.03.001
Lee JM, Kim BS, Lee H, Im G Il (2012) *In vivo* tracking of mesechymal stem cells using fluorescent nanoparticles in an osteochondral repair model. *Mol. Ther.* **20**: 1434–1442. https://doi.org/10.1038/mt.2012.60
Lee WY, Wei HJ, Lin WW, Yeh YC, Hwang SM, Wang JJ, Tsai MS, Chang Y, Sung HW (2011) Enhancement of cell retention and functional benefits in myocardial infarction using human amniotic-fluid stem-cell bodies enriched with endogenous ECM. *Biomaterials* **32**: 5558–5567. https://doi.org/10.1016/j.biomaterials.2011.04.031
Leibacher J, Henschler R (2016) Biodistribution, migration and homing of systemically applied mesenchymal stem/stromal cells Mesenchymal Stem/Stromal Cells – An update. *Stem Cell Res. Ther.* **7**: 7. https://doi.org/10.1186/s13287-015-0271-2
Lüttichau I Von, Notohamiprodjo M, Wechselberger A, Peters C, Henger A, Seliger C, Djafarzadeh R, Huss R, Nelson PJ (2005) Human adult CD34 − progenitor cells functionally express the chemokine receptors CCR1, CCR4, CCR7, CXCR5, and CCR10 but not CXCR4. *Stem Cells Dev.* **14**: 329–336. https://doi.org/10.1089/scd.2005.14.329
Majka M, Sułkowski M, Badyra B, Musialek P (2017) Concise review: mesenchymal stem cells in cardiovascular regeneration: emerging research directions and clinical applications. *Stem Cells Transl. Med.* **6**: 1859–1867. https://doi.org/10.1002/sctm.16-0484
Markel TA, Wang Y, Herrmann JL, Crisostomo PR, Wang M, Novotny NM, Herring CM, Tan J, Lahm T, Meldrum DR (2008) VEGF is critical for stem cell-mediated cardioprotection and a crucial paracrine factor for defining the age threshold in adult and neonatal stem cell function. *Am. J. Physiol. Circ. Physiol.* **295**: H2308–H2314. https://doi.org/10.1152/ajpheart.00565.2008
McGrail DJ, McAndrews KM, Dawson MR (2013) Biomechanical analysis predicts decreased human mesenchymal stem cell function before molecular differences. *Exp. Cell Res.* **319**: 684–696. https://doi.org/10.1016/j.yexcr.2012.11.017
Mirotsou M, Zhang Z, Deb A, Zhang L, Gnecchi M, Noiseux N, Mu H, Pachori A, Dzau V (2007) Secreted frizzled related protein 2 (Sfrp2) is the key Akt-mesenchymal stem cell-released paracrine factor mediating myocardial survival and repair. *Proc. Natl. Acad. Sci. U. S. A.* **104**: 1643–1648. https://doi.org/10.1073/pnas.0610024104
Molina EJ, Palma J, Gupta D, Torres D, Gaughan JP, Houser S, Macha M (2009) Reverse remodeling is associated with changes in extracellular matrix proteases and tissue inhibitors after mesenchymal stem cell (MSC) treatment of pressure overload hypertrophy. *J. Tissue Eng. Regen. Med.* **3**: 85–91. https://doi.org/10.1002/term.137
Murphy MB, Moncivais K, Caplan AI (2013) Mesenchymal stem cells: Environmentally responsive therapeutics for regenerative medicine. *Exp. Mol. Med.* **45**: e54. https://doi.org/10.1038/emm.2013.94
Nakajima H, Uchida K, Guerrero AR, Watanabe S, Sugita D, Takeura N, Yoshida A, Long G, Wright KT, Johnson WEB, Baba H (2012) Transplantation of mesenchymal stem cells promotes an alternative pathway of macrophage activation and functional recovery after spinal cord injury. *J. Neurotrauma* **29**: 1614–1625. https://doi.org/10.1089/neu.2011.2109
Nitzsche F, Müller C, Lukomska B, Jolkkonen J, Deten A, Boltze J (2017) Concise review: MSC adhesion cascade – insights into homing and transendothelial migration. *Stem Cells* **35**: 1446–1460. https://doi.org/10.1002/stem.2614
Olson MF, Sahai E (2009) The actin cytoskeleton in cancer cell motility. *Clin. Exp. Metastasis* **26**: 273–287. https://doi.org/10.1007/s10585-008-9174-2
Phinney DG, Prockop DJ (2007) Concise review: mesenchymal stem/multipotent stromal cells: the state of transdifferentiation and modes of tissue repair – current views. *Stem Cells* **25**: 2896–902. https://doi.org/10.1634/stemcells.2007-0637
Raab M, Swift J, Dingal PCDP, Shah P, Shin JW, Discher DE (2012) Crawling from soft to stiff matrix polarizes the cytoskeleton and phosphoregulates myosin-II heavy chain. *J. Cell Biol.* **199**: 669–683. https://doi.org/10.1083/jcb.201205056
Ries C, Egea V, Karow M, Kolb H, Jochum M, Neth P (2007) MMP-2, MT1-MMP, and TIMP-2 are essential for the invasive capacity of human mesenchymal stem cells: Differential regulation by inflammatory cytokines. *Blood* **109**: 4055–4063. https://doi.org/10.1182/blood-2006-10-051060
Rigol M, Solanes N, Roura S, Roqué M, Novensà L, Dantas AP, Martorell J, Sitges M, Ramírez J, Bayés-Genís A, Heras M (2014) Allogeneic adipose stem cell therapy in acute myocardial infarction. *Eur. J. Clin. Invest.* **44**: 83–92. https://doi.org/10.1111/eci.12195

Ringe J, Strassburg S, Neumann K, Endres M, Notter M, Burmester GR, Kaps C, Sittinger M (2007) Towards in situ tissue repair: Human mesenchymal stem cells express chemokine receptors CXCR1, CXCR2 and CCR2, and migrate upon stimulation with CXCL8 but not CCL2. *J. Cell. Biochem.* **101**: 135–146. https://doi.org/10.1002/jcb.21172

Rombouts WJC, Ploemacher RE (2003) Primary murine MSC show highly efficient homing to the bone marrow but lose homing ability following culture. *Leukemia* **17**: 160–170. https://doi.org/10.1038/sj.leu.2402763

Rosenthal N (2003) Prometheus's vulture and the stem-cell promise. *N. Engl. J. Med.* **349**: 267–274. https://doi.org/10.1056/NEJMra020849

Rudzka DA, Spennati G, McGarry DJ, Chim Y-H, Neilson M, Ptak A, Munro J, Kalna G, Hedley A, Moralli D, Green C, Mason S, Blyth K, Mullin M, Yin H, Olson MF (2019) Migration through physical constraints is enabled by MAPK-induced cell softening via actin cytoskeleton re-organization. *J. Cell Sci.* **132**: jcs224071. https://doi.org/10.1242/jcs.224071

Rüster B, Göttig S, Ludwig RJ, Bistrian R, Müller S, Seifried E, Gille J, Henschler R (2006) Mesenchymal stem cells display coordinated rolling and adhesion behavior on endothelial cells. *Blood* **108**: 3938–3944. https://doi.org/10.1182/blood-2006-05-025098

Sekula M, Domalik-Pyzik P, Morawska-Chochół A, Bobis-Wozowicz S, Karnas E, Noga S, Boruczkowski D, Adamiak M, Madeja Z, Chłopek J, Zuba-Surma EK (2017) Polylactide- and polycaprolactone-based substrates enhance angiogenic potential of human umbilical cord-derived mesenchymal stem cells *in vitro* – implications for cardiovascular repair. *Mater. Sci. Eng. C* **77**: 521–533. https://doi.org/10.1016/j.msec.2017.03.281

Siegel G, Kluba T, Hermanutz-Klein U, Bieback K, Northoff H, Schäfer R (2013) Phenotype, donor age and gender affect function of human bone marrow-derived mesenchymal stromal cells. *BMC Med.* **11**: 146. https://doi.org/10.1186/1741-7015-11-146

Sohni A, Verfaillie CM (2013) Mesenchymal stem cells migration homing and tracking. *Stem Cells Int.* **2013**: 130763. https://doi.org/10.1155/2013/130763

Sordi V, Malosio ML, Marchesi F, Mercalli A, Melzi R, Giordano T, Belmonte N, Ferrari G, Leone BE, Bertuzzi F, Zerbini G, Allavena P, Bonifacio E, Piemonti L (2005) Bone marrow mesenchymal stem cells express a restricted set of functionally active chemokine receptors capable of promoting migration to pancreatic islets. *Blood* **106**: 419–427. https://doi.org/10.1182/blood-2004-09-3507

Steingen C, Brenig F, Baumgartner L, Schmidt J, Schmidt A, Bloch W (2008) Characterization of key mechanisms in transmigration and invasion of mesenchymal stem cells. *J. Mol. Cell. Cardiol.* **44**: 1072–1084. https://doi.org/10.1016/j.yjmcc.2008.03.010

Su G, Liu L, Yang L, Mu Y, Guan L (2017) Homing of endogenous bone marrow mesenchymal stem cells to rat infarcted myocardium via ultrasound-mediated recombinant SDF-1α adenovirus in microbubbles. *Oncotarget* **9**: 477–487. https://doi.org/10.18632/oncotarget.23068

Szydlak R, Majka M, Lekka M, Kot M, Laidler P (2019) AFM-based Analysis of Wharton's jelly mesenchymal stem cells. *Int. J. Mol. Sci.* **20**: 18. https://doi.org/10.3390/ijms20184351

Trounson A, McDonald C (2015) Stem cell therapies in clinical trials: progress and challenges. *Cell Stem Cell* **17**: 11–22. https://doi.org/10.1016/j.stem.2015.06.007

Vincent LG, Choi YS, Alonso-Latorre B, Del Álamo JC, Engler AJ (2013) Mesenchymal stem cell durotaxis depends on substrate stiffness gradient strength. *Biotechnol. J.* **8**: 472–484. https://doi.org/10.1002/biot.201200205

Wang J, Jokerst J V. (2016) Stem cell imaging: tools to improve cell delivery and viability. *Stem Cells Int.* **2016**: 9240652. https://doi.org/10.1155/2016/9240652

Wang J, Jia H, Zhang B, Yin L, Mao F, Yu J, Ji C, Xu X, Yan Y, Xu W, Qian H (2018) HucMSC exosome-transported 14-3-3ζ prevents the injury of cisplatin to HK-2 cells by inducing autophagy *in vitro*. *Cytotherapy* **20**: 29–44. https://doi.org/10.1016/j.jcyt.2017.08.002

Ward MR, Abadeh A, Connelly KA (2018) Concise review: Rational use of mesenchymal stem cells in the treatment of ischemic heart disease. *Stem Cells Transl. Med.* **7**: 543–550. https://doi.org/10.1002/sctm.17-0210

Wei X, Yang X, Han ZP, Qu FF, Shao L, Shi YF (2013) Mesenchymal stem cells: A new trend for cell therapy. *Acta Pharmacol. Sin.* **34**: 747–754. https://doi.org/10.1038/aps.2013.50

Xu W, Mezencev R, Kim B, Wang L, McDonald J, Sulchek T (2012) Cell Stiffness is a biomarker of the metastatic potential of ovarian cancer cells. *PLoS One* **7**: e46609. https://doi.org/10.1371/journal.pone.0046609

Yagi H, Soto-Gutierrez A, Parekkadan B, Kitagawa Y, Tompkins RG, Kobayashi N, Yarmush ML (2010) Mesenchymal stem cells: Mechanisms of immunomodulation and homing. *Cell Transplant.* **19**: 667–679. https://doi.org/10.3727/096368910X508762

Yamahara K, Nagaya N (2007) Mesenchymal stem cells for the treatment of heart disease. *Regen. Med.* **2**: 107-109. https://doi.org/10.2217/17460751.2.2.107

Yang YHK, Ogando CR, Wang See C, Chang TY, Barabino GA (2018) Changes in phenotype and differentiation potential of human mesenchymal stem cells aging *in vitro*. *Stem Cell Res. Ther.* **9**: 131. https://doi.org/10.1186/s13287-018-0876-3

Yuan L, Sakamoto N, Song G, Sato M (2012) Migration of human mesenchymal stem cells under low shear stress mediated by mitogen-activated protein kinase signaling. *Stem Cells Dev.* **21**: 2520–2530. https://doi.org/10.1089/scd.2012.0010

Zachar L, Bačenková D, Rosocha J (2016) Activation, homing, and role of the mesenchymal stem cells in the inflammatory environment. *J. Inflamm. Res.* **9**: 231–240. https://doi.org/10.2147/JIR.S121994

Zeringer E, Barta T, Li M, Vlassov A V. (2015) Strategies for isolation of exosomes. *Cold Spring Harb. Protoc.* **2015**: 319–323. https://doi.org/10.1101/pdb.top074476

Zhang B, Luo Q, Chen Z, Sun J, Xu B, Ju Y, Song G (2015) Cyclic mechanical stretching promotes migration but inhibits invasion of rat bone marrow stromal cells. *Stem Cell Res.* **14**: 155–164. https://doi.org/10.1016/j.scr.2015.01.001

Zhang M, Mal N, Kiedrowski M, Chacko M, Askari AT, Popovic ZB, Koc ON, Penn MS (2007) SDF-1 expression by mesenchymal stem cells results in trophic support of cardiac myocytes after myocardial infarction. *FASEB J.* **21**: 3197–31207. https://doi.org/10.1096/fj.06-6558com

Zhao Y, Sun X, Cao W, Ma J, Sun L, Qian H, Zhu W, Xu W (2015) Exosomes derived from human umbilical cord mesenchymal stem cells relieve acute myocardial ischemic injury. *Stem Cells Int.* **2015**: 761643. https://doi.org/10.1155/2015/761643

Zhuang Y, Li D, Fu J, Shi Q, Lu Y, Ju X (2015) Comparison of biological properties of umbilical cord.derived mesenchymal stem cells from early and late passages: Immunomodulatory ability is enhanced in aged cells. *Mol. Med. Rep.* **11**: 166–174. https://doi.org/10.3892/mmr.2014.2755